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(54) Medicaments for treatment of emesis

(57) A pharmaceutical composition comprises 1, 2, 3, 9–tetrahydro–9–methyl–3–[(2–methyl–1H–imidazol–1–yl) methyl] – 4H–carbazol–4–one or a physiologically acceptable salt or solvate thereof and a cyclo-oxygenase inhibitor such as indomethacin or piroxicam.

The two active ingredients, which may be administered separately either simultaneously or sequentially, or may be combined in a single pharmaceutical preparation, are useful in the relief and/or prevention of nausea and vomiting.

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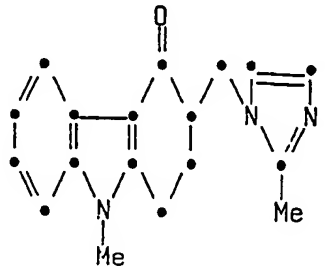
MEDICAMENTS

This invention relates to improvements in the treatment of gastrointestinal disorders. More particularly it relates to the use of a compound having antagonist activity at $5HT_3$ receptors in conjunction with a cyclo-oxygenase inhibitor in the treatment of emesis, and to pharmaceutical compositions containing the two compounds.

In our UK Patent Specification No. 2153821A we disclose inter alia 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl) methyl]-4H-carbazol-4-one which may be represented by the formula (I)



(I)

and physiologically acceptable salts, solvates and physiologically acceptable equivalents thereof.

In the aforementioned specification the compounds are described as potent and selective antagonists of 5- hydroxytryptamine (5HT) at 'neuronal' 5HT receptors of the type located on terminals of primary afferent nerves, and which are also present in the central nervous system. Receptors of this type are now designated $5HT_3$ receptors. The compounds are described as being of use in the treatment of a human or animal subject suffering from a condition caused by a disturbance of neuronal 5HT function, for example in the treatment of migraine pain or a psychotic disorder such as schizophrenia. The compounds may also be useful in the treatment of conditions such as anxiety, obesity and mania.

We have found, as described in our published European Patent Specification No. 226266, that the compounds disclosed in UK Patent Specification No. 2153821A additionally promote gastric emptying, and are thus useful in the treatment of conditions which may be relieved by the promotion of gastric emptying. Such conditions include gastric

stasis and symptoms of gastrointestinal dysfunction such as dyspepsia, reflux oesophagitis, peptic ulcer and flatulence.

According to published European Patent Specification No. 226266, the compounds have also been found to be anti-emetics, and may be used in the treatment or prevention of nausea and vomiting. The use of these compounds for the treatment of emesis is also described in published European Patent Specification No. 201165, which specification additionally refers to the use of the compounds for the treatment of irritable bowel syndrome.

Tests in animals have shown that the anti-emetic properties of the compound of formula (I) may be significantly enhanced by administering the compound in conjunction with a cyclo-oxygenase inhibitor. Such co-administration is particularly useful in the treatment of emesis resulting from chemotherapy, especially cancer chemotherapy involving the use of, for example, cisplatin.

The present invention thus provides a method of treating and/or preventing nausea and vomiting, which comprises administering to a human or animal subject the compound of formula (I) or a physiologically acceptable salt or solvate thereof, and a cyclo-oxygenase inhibitor.

According to another aspect the invention provides for the use of the compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for administration in conjunction with a cyclo-oxygenase inhibitor, for the treatment and/or prevention of nausea and vomiting.

The compound of formula (I) or a physiologically acceptable salt or solvate thereof, and the cyclo-oxygenase inhibitor, may be administered as a single pharmaceutical composition comprising effective amounts of the two active ingredients. Alternatively the two active ingredients may be co- administered in the form of two separate pharmaceutical compositions for simultaneous or sequential use.

Suitable physiologically acceptable salts of the carbazolone of formula (I) for use according to the invention include acid addition

salts formed with organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, citrates, fumarates and maleates. The solvates may, for example, be hydrates. A preferred form of the compound of formula (I) for use according to the invention is the hydrochloride, particularly in hydrated form, e.g. the dihydrate.

Suitable cyclo-oxygenase inhibitors that may be employed in the invention include systemic non-steroidal anti-inflammatory drugs such as, for example, aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac and tolmetin.

Indomethacin and, more particularly, piroxicam represent preferred cyclo-oxygenase inhibitors for use according to the invention.

The dose at which the carbazolone of formula (I) and the cyclo-oxygenase inhibitor may be administered to man (of approximately 70kg body weight) will depend upon the route of administration, the body weight of the patient, and the condition being treated and its severity.

A proposed dosage of the compound of formula (I) for use according to the invention is 0.05 to 25mg, more preferably 0.05 to 20mg, and most preferably 0.1 to 10mg per unit dose, expressed as the weight of free base. The unit dose may be administered, for example, 1 to 4 times per day.

The cyclo-oxygenase inhibitor may conveniently be administered at doses within the normal dosage range at which the compound is therapeutically effective, for example 200mg to 800mg of mefenamic acid, 50mg-1g of aspirin, 10 -100 mg of indomethacin and 5 - 50 mg of piroxicam per dosage unit taken one or more times daily in accordance with the normal dosage regime for the drug in question.

When the two active ingredients are administered as separate preparations, they may for example be given orally, parenterally (e.g. intramuscularly or, more particularly, intravenously) or rectally (e.g. by suppository), the cyclo-oxygenase inhibitor preferably being administered by the oral route.

The ability of cyclo-oxygenase inhibitors to enhance the anti-emetic properties of the carbazolone of formula (I) has been demonstrated in ferrets dosed with cisplatin, administering the drugs intraperitoneally, and observing the number of emetic episodes (vomits/retches) and/or the time during which emesis was inhibited.

According to a further aspect the invention provides a pharmaceutical composition, for use in human or veterinary medicine, comprising the compound of formula (I) or a physiologically acceptable salt or solvate thereof, and a cyclo-oxygenase inhibitor.

Compositions according to the invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients. Thus the compositions may, for example, be formulated for oral, buccal, parenteral or rectal administration. Compositions for rectal administration or, more particularly, for administration by the oral route (e.g. as tablets or capsules) are preferred.

Compositions for oral use such as tablets and capsules may be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). Tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of one or both active ingredients.

For parenteral administration the compositions may be presented in a form suitable for bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredients may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

For rectal administration the compositions may be formulated as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The pharmaceutical compositions of the invention may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the compound of formula (I) or a salt or solvate thereof and the cyclo-oxygenase inhibitor may be admixed together, if desired, with suitable excipients. Tablets may be prepared, for example, by direct compression of such a mixture. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine. Controlled release forms for oral or rectal administration may be formulated in a conventional manner associated with controlled release forms.

The compositions for use according to the invention may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredients. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Where the compound of formula (I) and the cyclo-oxygenase inhibitor are intended for administration as two separate compositions these may be presented in the form of, for example, a twin pack.

The following examples illustrate the preparation of the compound of formula (I). Temperatures are in ^{o}C.

Example 1

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one

A solution of 3-[(dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride (1.7g) in water (17ml) was treated with 2-methylimidazole (1.4g) and then heated under reflux for 20h. The cooled mixture was filtered and the residue washed with water (3x15ml) to give a product (1.7g) m.p. 221-221.5°. This material was recrystallised from methanol to give the title compound (1.4g) m.p. 231-232°.

Example 2

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (18.3g) in a hot mixture of isopropanol (90ml) and water (18.3ml) was treated with concentrated hydrochloric acid (6.25ml). The hot mixture was filtered and the filtrate diluted with isopropanol (90ml) and stirred at room temperature for 17h, cooled to 2° and the solid filtered off (21.6g). A sample (6g) was recrystallised from a mixture of water (6ml) and isopropanol (10ml) to give the title compound as a white crystalline solid (6g) m.p. 178.5-179.5°.

Analysis Found: C,59.45;H,6.45;N,11.5.

$C_{18}H_{19}N_3O.HCl.2H_2O$ requires C,59.1;H,6.6;N,11.5%.

Water assay Found: 10.23%

$C_{18}H_{19}N_3O.HCl.2H_2O$ requires 9.85%

The following examples illustrate pharmaceutical compositions according to the invention, containing 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate (Compound A) and piroxicam or mefenamic acid as the active ingredients. Compositions containing other physiologically acceptable salts or the compound of formula (I) in the form of its free base, or solvates thereof, and/or another cyclo-oxygenase inhibitor, may be formulated in a similar manner.

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such as direct compression or wet granulation.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques.

Direct Compression	mg/tablet
Compound A	5.0 *
Piroxicam	20.0
Anhydrous lactose NF	67.4
Microcrystalline cellulose NF	25.73
Pregelatinised starch NF	6.25
Magnesium stearate BP	0.62
Compression weight	125mg

* Equivalent to 4.0mg free base.

Compound A and the piroxicam are sieved through a suitable sieve and blended with the lactose, microcrystalline cellulose, pregelatinised starch and magnesium stearate. The resultant mix is compressed into tablets using a suitable tablet press fitted with 7.0mm normal concave punches.

Tablets of other strengths and/or combination of doses may be prepared by appropriate alterations in the amounts of the active ingredients and the excipients and using punches to suit.

Wet Granulation	mg/tablet
Compound A	10.0*
Mefenamic Acid BP	500.0
Lactose BP	206.0
Microcrystalline Cellulose USNF	40.0
Pregelatinised Starch USNF	40.0
Magnesium stearate BP	4.0
Compression weight	800 mg

* Equivalent to 8.0mg free base

Compound A and the mefenamic acid are sieved through a suitable sieve and blended with the lactose, microcrystalline cellulose and pregelatinised starch. The blend is granulated with Purified Water BP and the granules are dried. The granules are screened and blended with the magnesium stearate. The granules are compressed into tablets using suitable punches.

Tablets of other strengths and/or combination of doses may be prepared by appropriate alterations in the amounts of the active ingredients and the excipients and using punches to suit.

CAPSULES

	mg/capsule
Compound A	10.00*
Piroxicam	20.0
Pregelatinised Starch USNF	54.625
Magnesium stearate BP	0.375
Fill weight	85.00

* Equivalent to 8.0mg free base.

Compound A and the piroxicam are sieved through a 250µm sieve and blended with the pregelatinised starch and magnesium stearate. The resultant mix is filled into size 3 hard gelatin capsules using a suitable filling machine.

Capsules of other strengths and/or combination of doses may be prepared by appropriate alterations in the amounts of the active ingredients and the excipients, using appropriately sized capsules.

CLAIMS:

1. A pharmaceutical composition for use in human or veterinary medicine comprising 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or solvate thereof and a cyclo-oxygenase inhibitor.

2. A pharmaceutical composition as claimed in Claim 1 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is used in the form of a hydrochloride salt.

3. A pharmaceutical composition as claimed in Claim 2 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is used in the form of the hydrochloride dihydrate.

4. A pharmaceutical composition as claimed in any of Claims 1 to 3 wherein the cyclo-oxygenase inhibitor is a systemic non-steroidal anti-inflammatory drug.

5. A pharmaceutical composition as claimed in any of Claims 1 to 3 wherein the cyclo-oxygenase inhibitor is aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac or tolmetin.

6. A pharmaceutical composition as claimed in any of Claims 1 to 3 wherein the cyclo-oxygenase inhibitor is indomethacin or piroxicam.

7. A pharmaceutical composition as claimed in any of

Claims 1 to 3 in unit dose form containing 0.05 to 25mg per unit dose of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one expressed as the weight of free base and 10 to 100 mg of indomethacin or 5 to 50 mg of piroxicam per unit dose.

8. A pharmaceutical composition as claimed in Claim 7 in which the unit dose of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is 0.1 to 10mg.

9. A pharmaceutical composition as claimed in any of Claims 1 to 8 in a form adapted for oral, parenteral or rectal administration.

10. A pharmaceutical composition as claimed in Claim 9 for oral administration in the form of tablets.

11. A pharmaceutical composition as claimed in any of Claims 1 to 10 containing at least one physiologically acceptable carrier or excipient.

12. A method for the manufacture of a pharmaceutical composition as claimed in any of Claims 1 to 11 which comprises processing the components by conventional techniques to form a pharmaceutical composition.

13. The use of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for administration in conjunction with a cyclo-oxygenase inhibitor in the treatment and/or prevention of nausea and vomiting.

14. The use as claimed in Claim 13 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-

yl)methyl]-4H-carbazol-4-one is used in the form of a hydrochloride salt.

15. The use as claimed in Claim 14 wherein the 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is used in the form of the hydrochloride dihydrate.

16. The use as claimed in any of Claims 13 to 15 wherein the cyclo-oxygenase inhibitor is a systemic non-steroidal anti-inflammatory drug.

17. The use as claimed in any of Claims 13 to 15 wherein the cyclo-oxygenase inhibitor is aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac or tolmetin.

18. The use as claimed in any of Claims 13 to 15 wherein the cyclo-oxygenase inhibitor is indomethacin or piroxicam.

19. The use as claimed in any of Claims 13 to 15 wherein the medicament is in unit dose form containing 0.05 to 25 mg per unit dose of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one expressed as the weight of free base for administration in conjunction with indomethacin in a unit dose of 10 to 100mg or piroxicam in a unit dose of 5 to 50mg.

20. The use as claimed in Claim 19 in which the unit dose of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one is 0.1 to 10mg.

21. The use as claimed in any of Claims 13 to 20 wherein the medicament is in a form adapted for oral, parenteral or rectal administration.

22. The use as claimed in Claim 21 wherein the medicament is for oral administration in the form of tablets.

23. The use as claimed in any of Claims 13 to 22 wherein the medicament is for administration in conjunction with a cyclo-oxygenase inhibitor but separately therefrom.

24. The use as claimed in Claim 23 wherein the cyclo-oxygenase inhibitor is in a form adapted for oral administration.

25. The use as claimed in any of Claims 13 to 24 wherein the medicament contains at least one physiologically acceptable carrier or excipient.

26. A twin pack comprising separate unit dose forms of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one or a physiologically acceptable salt or solvate thereof and a cyclo-oxygenase inhibitor in association for separate administration.

27. A twin pack as claimed in Claim 26 wherein the cyclo-oxygenase inhibitor is indomethacin or piroxicam.